



Clinical Pharmacology & Toxicology Pearl of the Week

~ Clozapine ~

- ✓ Clozapine is an atypical antipsychotic most often reserved for use in patients who have treatment-resistant schizophrenia. It has a greater effect on negative symptoms and in patients with suicidal ideation than other antipsychotic drugs.
- ✓ Clozapine has the greatest association with causing weight gain (on average 30lbs in those on long-term therapy). It also causes hyperglycemia and insulin resistance in about 30-40% of patients, as well as hypertension and hyperlipidemia.

Clozapine Pharmacokinetics

- Absorption – Well absorbed with an oral bioavailability of 50% following first-pass metabolism
- Distribution – Highly variable volume of distribution (1.6 – 7 L/kg).
- Metabolism - Clozapine is extensively metabolized in the liver by CYP1A2 (major), CYP2D6 and CYP3A4. Most metabolites are inactive, although one (N-desmethylozapine) has some limited activity at dopamine receptors.
- Elimination – elimination half-life of 12-14 hours, with a mix of renal (50%) and fecal (30%) elimination routes for metabolites.

Clozapine is associated with common adverse effects, such as:

- hypersalivation
- urinary incontinence
- constipation
- sedation
- cholinergic rebound upon its cessation (should be tapered off if possible)

Clozapine is known to cause rare but serious adverse effects including:

- severe neutropenia
 - seizures
 - myocarditis
 - increased mortality in elderly patients with dementia-related psychosis
 - increased risk of orthostatic hypotension, bradycardia, and syncope
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- ✓ In patients on clozapine, it is important to monitor a CBC, blood sugar & HbA1c% and a fasting lipid panel.
 - ✓ Maintaining a high degree of suspicion for drug-related adverse effects in patients on clozapine is essential.
 - ✓ Therapeutic drug monitoring with plasma levels of clozapine and norclozapine may aid in dose titration for patients with altered pharmacokinetics due to CYP enzyme genetic polymorphisms.

References:

1. Jann, MW, Grimsley, SR, Gray EC et al. Pharmacokinetics and Pharmacodynamics of Clozapine. Clin. Pharmacokinet.(1993)24:161.
2. Freudenreich O and McAvoy J. Guidelines for prescribing clozapine in schizophrenia.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the [Alberta Referral Directory](#) (ARD) by searching “Pharmacology” from the ARD home page. Click [HERE](#) for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in [Alberta Referral Directory](#) (ARD) by searching “Toxicology” from the ARD home page.

More CPT Pearls of the Week can be found [HERE](#).

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